TABLE 2

Average Release Rates of Fentanyl and Ethanol
from Annealed vs. Non-annealed Systems

MEMBRANE	FENTANYL RELEASE RATE ($\mu g/cm^2$ hr)	ETHANOL RELEASE RATE ($\mu g/cm^2$ hr)
2 mil control	3.6	35
2 mil annealed	4.6	47
3 mil control	3.3	20
3 mil annealed	4.0	39
3.5 mil control	3.2	29
3.5 mil annealed	4.6	35

EXAMPLE 3

[00076] The effect of annealing temperature on fentanyl flux was studied. Systems were made according to the procedure set forth in Example 1. The rate controlling membranes were annealed at various temperatures ranging from 45 - 80°C for two hours. The flux of fentanyl from these systems was then measured by the skin flux experiments described in Example 1. The results are shown in Figure 9, which is a plot of the average fentanyl flux ($\mu g/cm^2$ hr) over the period 2-29 hours following application of the system vs. temperature of the annealing process. As seen in Figure 9, the average flux of fentanyl during the 2-29 hour period increased substantially linearly with increasing annealing temperature.

EXAMPLE 4

[00077] The effect of storage on the permeability stability of an EVA membrane was investigated. Donor solutions were prepared by adding fentanyl base to a mixture of 95% ethanol and purified water. 2% of hydroxyethyl cellulose gelling agent was added slowly to the solution with stirring and mixed until a smooth gel was obtained (approximately 1 hour). Flux experiments were performed to measure the flux of fentanyl from the

donor solution through annealed EVA film containing 9% vinyl acetate (EVA 9) and compared to fentanyl flux through a non-annealed EVA 9 membrane. The EVA 9 membranes were annealed at 60° C for 2 hours. Membrane 1 was annealed 15 months prior to the flux experiment while membrane 2 was annealed on the day of the flux experiment.

[00078] The experiment was carried out using standard glass diffusion cells which consist of a donor compartment and a receptor compartment. The rate controlling membrane was placed in each diffusion cell in a horizontal position between a lower capped receptor compartment and an upper capped donor compartment. The receptor compartment has both a venting tube (uncapped) and a sampling port (capped). An O-ring was positioned between the membrane and the donor compartment, and a clamp held the compartments together. The receptor solution, 0.05M phosphate buffer, pH 6.5, was added to each receptor compartment. The cells were placed in a temperature controlled water bath shaker at 35°C and allowed to come to temperature before the donor solution was added. The donor solution comprised fentanyl gel with a large excess of fentanyl in order to maintain constant steady state flux throughout the 30 hour sampling period.

[00079] At each time interval, the receptor solution was removed from the test cell and replaced with an equal volume of fresh receptor solution previously equilibrated at 35°C. The receptor solutions for each time interval were then assayed for fentanyl by HPLC analysis to calculate the permeation rate of fentanyl through the membrane from the donor solutions. From the drug concentration and the volume of the receptor solutions, the area of permeation and the time interval, the flux of the drug through the rate controlling membranes was calculated as follows: (drug concentration X volume of receptor)/(area x time) = flux ($\mu g/cm^2$ hr).

TABLE 3

Effect of Storage on EVA 9 Membrane Permeability

MEMBRANE	ANNEALLING	FENTANYL FLUX (μg/cm^2 hr)
membrane 1	60° C for 2 hours	11.0
membrane 2	60° C for 2 hours	10.8
membrane 3	none	6.5

As seen in Table 3, the permeability of membrane 1 was stable after 15 months storage at room temperature.

EXAMPLE 5

[00080] Tests were done to study the effects of annealing on high density polyethylene (HDPE) films using nicotine as a model drug. Drug reservoirs were prepared by mixing 60 wt% ethylene vinyl acetate (39% vinyl acetate) and 40 wt% nicotine base and were allowed to equilibrate to room temperature. 10 cm^2 patches were prepared by placing approximately 0.4 grams of the drug reservoir on the heat sealable (silver side) of a Scotchpak polyester backing using a syringe. HDPE resins (LR723, LR734 and LS901, Millenium, Texas) were cast into films which were then heated in an oven at 70°C for a period of two hours. An HDPE film to be tested was placed over the drug reservoir mixture, and a piece of Teflon film was placed over the HDPE film and the films were heat sealed together. Finished systems were cut from the prepared laminate by hand punching around the heat sealed zone.

[00081] *In vitro* release rate experiments were performed to measure the release of nicotine through annealed HDPE film and compared to nicotine release through a non-annealed HDPE membrane. The release liner was removed and the device was then mounted on a Teflon® holder of a release